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Review

Implantable biosensors and their contribution to the future of precision medicine

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ABSTRACT

Precision medicine can be defined as the prevention, investigation and treatment of diseases taking individual variability into account. There are multiple ways in which the field of precision medicine may be advanced; however, recent innovations in the fields of electronics and microfabrication techniques have led to an increased interest in the use of implantable biosensors in precision medicine. Implantable biosensors are an important class of biosensors because of their ability to provide continuous data on the levels of a target analyte; this enables trends and changes in analyte levels over time to be monitored without any need for intervention from either the patient or clinician. As such, implantable biosensors have great potential in the diagnosis, monitoring, management and treatment of a variety of disease conditions. In this review, we describe precision medicine and the role implantable biosensors may have in this field, along with challenges in their clinical implementation due to the host immune responses they elicit within the body.

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Introduction

Precision and personalised medicine are interchangeable terms, with similar concepts. Due to concerns among clinicians and scientists that the term “personalised” could be misunderstood, leading patients to believe that unique treatments/drugs were being developed specifically for each individual, the term personalised medicine has now predominately been replaced with precision medicine (Biesecker et al., 2011; Katsnelson, 2013). Precision medicine is defined as the prevention, investigation and treatment of diseases taking individual variability into account. These factors include disease biomarkers, molecular signatures, phenotype, environment and lifestyle (Ghasemi et al., 2016). This approach allows individual patients to be classified into sub-populations that differ in their susceptibility to a particular disease, prognosis and response to treatment (Bu et al., 2016). Precision medicine can therefore help to identify patients most

likely to benefit from a specific treatment, thus improving clinical outcomes whilst reducing side effects (Penet et al., 2014).

Even though precision medicine is not a new concept, it has gained increased awareness and momentum in recent years, aided by world leaders such as the former President of the United States Barack Obama, who announced the “Precision Medicine Initiative” at the beginning of 2015. This initiative aimed “to bring us closer to curing diseases like cancer and diabetes – and to give us all access to the personalised information we need to keep ourselves and our families healthier” (Collins and Varmus 2015).

Although the role of precision medicine in everyday treatment is currently limited, dedicated centres, such as The Centre for Personalised Medicine in the UK and The Personalised Medicine Coalition in the USA, should make the integration of precision medicine into everyday healthcare practices more widespread in the coming years (Carrasco-Ramiro et al., 2017). However, cross disciplinary approaches involving engineering and chemistry may be needed to make significant progress. While the application of precision medicine is currently more focused on humans, its concepts are equally applicable in the treatment of veterinary patients.

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Implantable biosensors

The physiology of disease tissue can be markedly different to that of healthy tissue, with diseases such as cancer or diabetes mellitus leading to measurable changes within the body. Methodology that could provide continuous data on the levels of a target analyte, enabling trends and changes in concentrations over time to be analysed, without any need for intervention from the patient or clinician, would be very valuable (Vaddiraju et al., 2010). As such, implantable medical devices have great potential in the diagnosis, monitoring, management and treatment of a variety of disease conditions (Cavallini et al., 2015) (Fig. 1).

Advances in the fields of electronics and microfabrication techniques have caused increased interest in the use of implantable medical devices in precision medicine. Biosensors are analytical devices containing a biological sensing element that transforms a biological response into electrical signals (Turner, 2013; Mehrotra, 2016). Biosensors have many different applications, from environmental monitoring and food safety, to security and defence; however, the use of biosensors for medical diagnostics represents the largest driver for biosensor development and application today (Turner, 2013).

Implantable electrochemical biosensors

Biosensors are composed of two main parts; a bio-recognition element and a transducer. The bio-recognition element of the sensor identifies a target analyte, while a transducer converts the output from the molecular recognition into an electrical signal (Thévenot et al., 2001). Different molecular recognition elements

can be employed, including enzymes, nucleic acids, antibodies, proteins and peptides. Electrochemical biosensors have electrodes as their transduction element (Thévenot et al., 2001).

Clark is credited with developing the first biosensor in 1962; this 'enzyme electrode' (Clark and Lyons, 1962) was a concept built on his earlier invention the Clark oxygen electrode (Clark, 1959). Having enzymes as the molecular recognition element depends on the catalytic conversion of an enzymatic substrate to a product. Because enzymes have highly specific binding pockets, enzyme electrodes have high selectivity against their chosen analyte (Zhu et al., 2015). Clark's paper described the electrochemical detection of O₂ or CO₂ by immobilised enzymes. In one example, the enzyme glucose oxidase (GOx) was entrapped on a platinum O₂ electrode over a semi-permeable dialysis membrane, with the amount of O₂ consumed by the electrode acting as an indirect measure of glucose levels (Clark and Lyons, 1962).

Electrochemical biosensors have the potential to offer the sensitive and rapid detection of a wide range of biomarkers; their relative fabrication simplicity, amenability to miniaturisation, along with the reduced cost of instrumentation, has also furthered interest in their development (Kokkinos et al., 2016).

Biosensors and metabolic diseases

One of the first major successful applications of implantable biosensors was in the field of metabolic diseases, specifically diabetes mellitus. Despite advances in insulin therapy delivery and the development of more physiological insulin preparations (Home, 2012), the avoidance of hypoglycaemic episodes still remains a challenge (Cryer, 2015). Blood glucose measurements

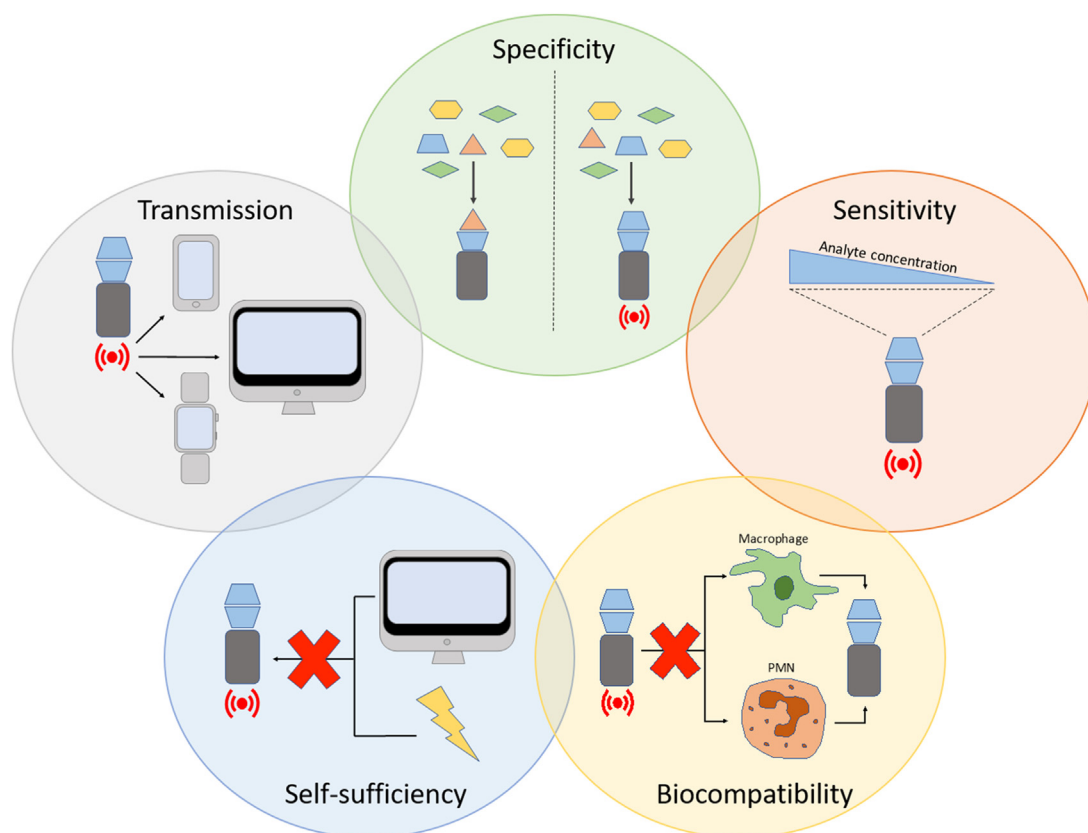


Fig. 1. Diagram showing the criteria that an ideal implantable biosensor should possess. These requirements include: sensitivity and specificity (the biosensor must be able to operate within the therapeutic range of the target substance whilst in the presence of complex solutions e.g. interstitial fluid or blood), biostability and biocompatibility (negative immune reactions may cause the device to become non-functional), self-sufficiency (in terms of power supply and control from external devices) and transmission (the signal output transmitted to an external communication device should be in a meaningful form for ease of use for the patient/clinician).

are traditionally performed with the blood from pin-prick samples and amperometric home-use glucose sensors. Regular blood sampling can be painful and time consuming, causing psychological distress and poor patient compliance (Rubin and Peyrot, 2001); non-compliance among diabetic patients has been estimated in the range of 50–80% (Chatterjee, 2006). Similar issues are encountered in veterinary patients. Commonly used monitoring methods to manage diabetic dogs and cats are classified as direct or indirect. Indirect monitoring includes the assessment of water intake, quantification of glycosuria and ketonuria, and measurement of glycosylated protein concentrations, whereas direct monitoring includes serial or continuous blood glucose measurements (Cook, 2012). Although serial blood glucose measurements are the mainstay monitoring method used in clinical practice, this can be problematic due to large day-to-day variations in blood glucose levels in dogs (Fleeman and Rand, 2003) and stress hyperglycaemia in cats (Rand et al., 2002). Owners predominately rely on home-use urine tests to monitor glucose levels; however, these urine tests only reflect the glucose levels over a large time frame, and transient hypoglycaemia may be masked by hyperglycaemic periods. Even animals whose diabetes is under control and experience several hours of euglycaemia will likely be glycosuric for several hours a day (Cook, 2012). The Somogyi effect is also seen in both dogs and cats, whereby sustained rebound hyperglycaemia occurs after an acute decrease in blood glucose levels; insulin levels therefore should not be increased based on persistent hyperglycaemia. To overcome some of the issues outlined with blood glucose measurements in dogs and cats, glycosylated proteins such as glycosylated haemoglobin and fructosamine concentrations can be measured to give a quantitative indirect assessment of diabetes diagnosis and management (Thoresen and Bredal, 1996; Loste and Marca, 2001; Cook, 2012).

The development of continuous glucose monitoring (CGM) over the last 15 years aims to provide real-time interstitial glucose readings, alerting patients to impending hypo- and hyperglycaemic episodes. Although CGM systems for veterinary patients are not in mainstream use, they have been successfully used in clinics (Davison et al., 2003; Wiedmeyer et al., 2003; Wiedmeyer and DeClue, 2008). CGM systems can be connected with subcutaneous insulin infusion systems, creating sensor augmented pumps with the automated administration of insulin, acting as an artificial pancreas (Cengiz et al., 2011; Kropff and Devries, 2016; Bally et al., 2017).

Continuous glucose-monitoring systems using long-term (> 90 days) fully implantable sensors have now been brought to the market (Eversense, Senseonics Inc.) (Dehennin et al., 2015). This system uses an implanted glucose sensor, a removable wearable smart transmitter and a mobile app to display real-time glucose measurements. Long-term implantable CGM systems are beneficial to patients as the number of times the sensor needs to be replaced is decreased, thus reducing warm-up procedures and the risk of sensor damage from each implantation (Kropff and Devries, 2016).

These types of amperometric enzyme-based biosensors have also been utilised in the field of experimental neuroscience. Regulatory disturbances in brain energy metabolism (particularly in respect to glucose, lactate and pyruvate levels) can have a negative impact on cognitive learning and memory (Hertz and Gibbs, 2009), and is thought to be involved in multiple neurological diseases/disorders (Moretti et al., 2003; Cloix and Hevor, 2009; Kapogiannis and Mattson, 2011). An amperometric enzyme-based multiplex biosensor device (MBD) for the monitoring of brain glucose, lactate and pyruvate, has been developed using glucose oxidase, lactate oxidase and pyruvate oxidase respectively at the electrode surface. This biosensor was implanted into the medial prefrontal cortex of anaesthetised rats, where researchers showed

that the biosensor was able to continuously and simultaneously monitor these three metabolism-related biomarkers in a specific brain region with temporal and spatial accuracy (Cordeiro et al., 2015).

Biotelemetry

Biotelemetry (the remote measurement of an activity, function or condition) utilises implantable technology as a means of obtaining data in an experimental setting in conscious, unrestrained animals. Electromyogram (EMG), electroencephalogram (EEG), electrocardiogram (ECG), heart rate, blood pressure, body temperature, activity and circadian rhythm data can be collected using biotelemetry techniques (Bertram and Lothman, 1991; Kramer et al., 2001; Güler and Übeyli, 2002; Kramer and Kinter, 2003; Bastlund et al., 2004; Weiergräber et al., 2005; Bassett et al., 2014; Lundt et al., 2016). It is thought that information obtained from conscious, unrestrained animals is likely to be more comparable to that seen in humans, in contrast to classically derived data from anaesthetised or restrained animals (Kramer and Kinter, 2003). Wireless radiotelemetry has been used in a variety of laboratory animals, including mice as small as 20 g and fish, with transmitters commonly implanted either intraperitoneally, subcutaneously or between abdominal muscle layers (Snelderwaard et al., 2006; Bassett et al., 2014; Lundt et al., 2016). Biotelemetry has been shown to be of value in the characterisation of various animal models of human diseases, including epilepsy, sleep disorders, neurodegenerative and neuropsychiatric disorders (Güler and Übeyli, 2002; Bastlund et al., 2004; Williams et al., 2006). This technique also has a role in the investigation of the pharmacokinetic, pharmacodynamic and toxicological properties of drugs, helping to determine their safety margins and efficacy. For example, EEG recordings can be used to assess a drug's effect on the central nervous system, including the detection of seizure activity (Bassett et al., 2014), whereas ECG, heart rate and blood pressure can be used to investigate the effects of cardiac drugs (Anderson et al., 1999). One study, using radiotelemetry combined with an automatic blood sampler and urine analysis, demonstrated the feasibility of recording multiple telemetric and non-telemetric physiological parameters simultaneously (Kamendi et al., 2010).

Biosensors and drug delivery

Different types of biosensors featuring drug delivery systems have been developed with the ability to deliver drugs in response to biosensor readings. Micro-electromechanical systems (MEMS)-based drug delivery devices are one example, with BioMEMS defined as a class of MEMS which incorporate biological entities or have a biological application (Menon et al., 2013). The use of techniques created for the electronics industry has enabled the production of the micro-reservoirs, micropumps, valves and sensors (Staples et al., 2006; Ngoepe et al., 2013) needed to make miniaturised devices. These devices have the ability to sense, monitor, mix, pump and control the flow of small amounts of fluid (Nisar et al., 2008), some of which are commercially available (Ngoepe et al., 2013). Smart polymers, which have been produced to go through structural alterations when subjected to changes to external stimuli such as temperature or pH (Ngoepe et al., 2013) can also be used as biosensors. They have the ability to deliver drugs when needed. One such example is the attachment of both glucose oxidase and insulin within a hydrogel that is responsive to changes in pH, enabling this smart polymer to act both as a sensor of glucose concentration and as a drug delivery vehicle for insulin (Traitel et al., 2000). These types of biosensor-drug delivery systems can reduce the risk of overdosing/underdosing a patient

whilst allowing the patient to receive the drug at a specific time point (Smolensky and Peppas, 2007).

Implantable drug delivery systems have also great potential for use in diseases in which treatment regimens are difficult to implement. Osteoporosis affects bone density leading to weakened/fragile bones. One treatment option for this condition is the daily injection of human parathyroid hormone fragment (1-34) [hPTH(1-34)] as an anabolic therapy, stimulating osteoblastic bone formation (Cosman, 2006). This therapy can last up to 2 years, which makes patient compliance problematic (Papaioannou et al., 2007). The first-in-human testing of a wirelessly controlled drug delivery microchip was used in the treatment of osteoporosis (Farra et al., 2012); the device consisted of silicon chips with multiple individual reservoirs filled with concentrated hPTH(1-34) solution. Pharmacokinetic evaluation showed that the microchip produced similar results to multiple daily injections, with bone marker evaluation indicating that bone formation increased even though a fibrous capsule developed around the implanted device. This study is an excellent example of where implantable devices can be utilised to overcome difficult treatment regimens and poor patient compliance.

Implantable technology and cancer monitoring/treatment

Tumour physiology differs markedly from normal tissue physiology. Tumours are characterised by areas of O₂ depletion (hypoxia and anoxia), glucose and energy deprivation, extracellular acidosis, high lactate levels and interstitial hypertension. This unique tumour microenvironment (TME) is largely determined by an abnormal tumour vasculature and its heterogeneous microcirculation (Vaupel, 2004).

Biosensors and the clinical monitoring of cancer progression

The TME strongly influences a tumours response to radiotherapy (RT) and chemotherapy; therefore, monitoring the TME for certain biomarkers, pH, O₂, cancer metabolites or chemotherapeutic drug concentrations could allow observation of the treatment response, and improve the detection of recurrence or metastasis. An implantable diagnostic device placed within the tumour, or the surrounding tissue, following surgery or at the time of biopsy would be one potential method to achieve this kind of precision monitoring (Sedlacek et al., 2002; Daniel et al., 2009). This would be especially useful in areas where imaging (e.g. MRI/CT) makes it difficult to distinguish between the tumour recurrence, fibrosis, necrosis or benign lesions from previous surgery and/or chemoradiotherapy treatment (e.g. gliomas) (Verma et al., 2013). The first *in vivo* description of such a device was used to detect soluble cancer biomarkers (the β subunit of human chorionic gonadotrophin) in mice, using nanoparticle magnetic relaxation switches (MRSw) enclosed within an implantable device by a semipermeable membrane (Daniel et al., 2009).

Tumour microenvironment and hypoxia

Tissue oxygenation is an important component of many cancers (Vaupel, 2004; Bertout et al., 2008). The mechanisms involved in the development of hypoxia in solid tumours include perfusion-limited, diffusion-limited and anaemic hypoxia (Secomb et al., 2012; Vaupel and Mayer, 2014) (Fig. 2). Hypoxia was one of the first recognised modifiers of treatment outcomes, with a multitude of studies published from 1909 onwards suggesting that O₂ levels had an influence on the radiosensitivity of cells (Bertout et al., 2008). Papers published in the early 1950s confirmed this (Gray et al., 1953). At a given dose of radiation, cancer cells in low O₂ conditions

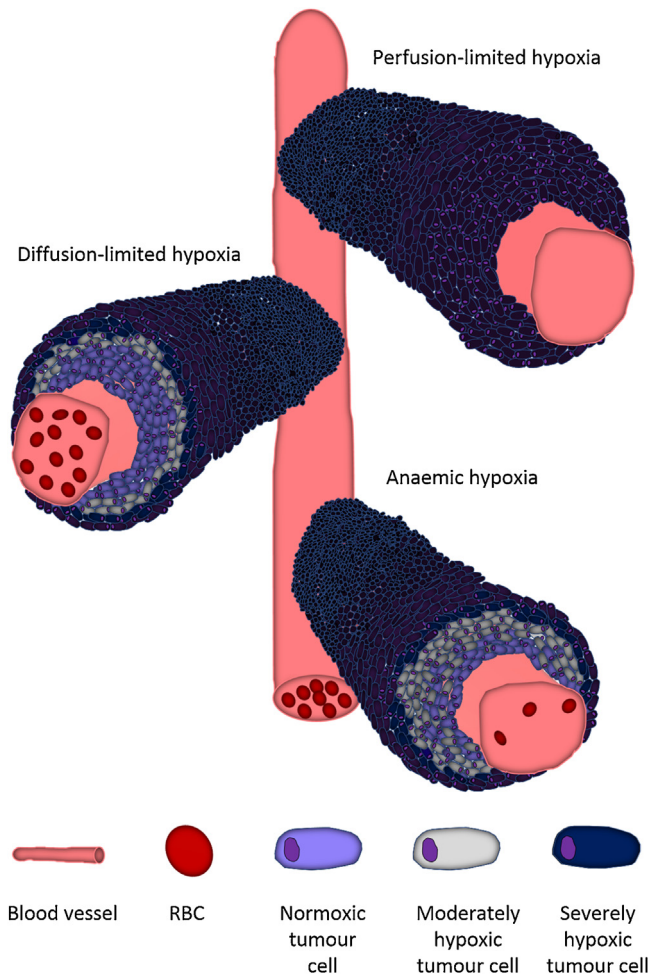


Fig. 2. Diagram outlining the mechanisms of hypoxia development in solid tumours. Hypoxia is defined as a state of reduced O₂ availability. Most mammalian tissues function in O₂ concentrations ranging from 2 to 9%, with O₂ concentrations <2% defined as hypoxic. It is estimated that up to 60% of locally advanced solid tumours have heterogeneously distributed hypoxic tissue areas. Perfusion-limited hypoxia is brought about by structural and functional abnormalities of the tumour microvessels, leading to disturbances in blood flow and causing acute/transient hypoxia. Diffusion-limited hypoxia results from the viable aerobic tumour cells around the blood vessels utilising the available O₂, giving rise to chronic hypoxia in areas beyond the diffusion distance of O₂ (150–180 μ m). Anaemic hypoxia is caused by tumour-associated and/or therapy-induced anaemia, leading to a reduced blood O₂ transport capacity.

can tolerate a dose 2–3 times higher than aerobic cells. This O₂ enhancement effect was highlighted in a large international study which demonstrated that the pre-treatment tumour O₂ status for patients with head and neck cancer was a prognostic factor for survival after RT (+/– surgery, chemotherapy, or radiosensitizer) (Nordsmark et al., 2005).

Tumour functional imaging and implantable technology

To target hypoxic tumour areas, clinicians need to be able to detect them. There are several approaches used for detection which can be divided into indirect and direct methods. Molecular reporters of O₂, which form adducts with intracellular macromolecules at low O₂ levels, can be detected through immunohistochemistry and represent an indirect method of hypoxic detection, as does the assessment of genes and proteins whose levels are regulated by O₂ levels (such as HIF-1 and CAIX) (Le and Courter, 2008; Meehan et al., 2017). However, indirect methods only allow the analysis of small portions of a tumour at any one

time, meaning that the hypoxic heterogeneity of the entire tumour is not represented. Also, the extent of hypoxia, and its changing distribution throughout the tumour at the time of treatment, are not given by these methods. Direct measurements of O₂ can be made using polarographic electrodes, such as the Eppendorf O₂ electrode (Vaupel et al., 1991), but because of their invasive nature these are not used clinically. Non-invasive imaging of tumour hypoxia, through PET and MRI, allows clinicians to analyse tumour hypoxia across the whole tumour volume (Hammond et al., 2014). However, the images produced are static measurements that only provide a snapshot of hypoxia at the time of analysis.

Therefore, despite advances, approaches that give an accurate 3D map of hypoxic areas within the entire tumour volume are not available. As a result, there is an unmet clinical need for an implantable biosensor that gives readings of the hypoxic areas/levels in a tumour at the time of treatment, along with the spatial and temporal changes that can occur. The Implantable Microsystems for Personalised Anti-Cancer Therapy (IMPACT) project aims to produce such a device.¹ The purpose of the project is to manufacture implantable wireless sensors for the real-time monitoring of tumour O₂ levels, thus allowing RT to be delivered at the most effective location and time (Marland et al., 2018). Studies testing the manufactured sensors from the IMPACT project are currently underway in animal models; should these produce positive results, validation of the biosensors will be required in clinical trials. If the IMPACT project is successful, it may lead to the production of a biosensor that could prove to be a formidable tool in realising biologically adapted RT.

Cancer treatment and implantable technology

Short-term implantable devices have been developed for high-throughput drug sensitivity testing within solid tumours. A device containing multiple reservoirs capable of releasing drugs into spatially distinct tumour regions at concentrations that could be achieved systemically has been described (Jonas et al., 2015). Removal of tumour tissue surrounding the device 24 h after implantation allowed assessment of each drug's anti-neoplastic effect through immunohistochemical analysis (Jonas et al., 2015). These types of devices could be employed to release drugs directly within the TME, negating potential toxic systemic side effects, while also aiding the identification of a patient's optimal drug treatment before definitive systemic treatment commences.

Implantable technology could play an important role in the treatment of brain tumours. The presence of the blood-brain barrier is a significant limitation to the development of more effective brain tumour therapies as it prevents the transfer of non-lipid soluble molecules and particles larger than 500 Da in size into the brain (Groothuis et al., 2000). Systemic toxicity for commonly used chemotherapeutic agents is often reached before obtaining a therapeutically effective concentration in the brain. MEMS-based drug delivery systems have been used experimentally to deliver drugs directly to the brain, thus overcoming the issues associated with the blood brain barrier to achieve therapeutic doses of drugs within primary brain tumours such as gliomas (Masi et al., 2012).

Radiotherapy plays a major role in the treatment of many cancers. However, the clinical success of RT depends on the accuracy of delivering the calculated dose to the desired area, with tumour radiosensitivity also having an influence on treatment response. Implantable dosimeters, such as the dose verification system (DVS), can verify the radiation dose received by the target volume for each treatment session/fraction (Beyer et al., 2008).

This DVS has undergone clinical testing and received FDA approval for use in breast and prostate cancer and could allow radiation oncologists to optimise radiation treatment on an individual basis.

Biocompatibility and the foreign body response

For implantable sensors to be used clinically, they must be characterised in terms of their biocompatibility; this should incorporate both bio-functionality (does the sensor perform correctly) and biosafety (the extent of local and systemic tissue responses and the absence of carcinogenesis, mutagenesis and cytotoxicity) (Arshady, 2003; Schoen and Anderson, 2004; Morais et al., 2010). Unfortunately, following implantation biosensors typically lose functionality over time; this detrimental effect is largely due to biofouling (non-specific cell/protein absorption) that occurs locally around the biosensor and results in a tissue reaction known as the foreign body response (FBR) (Anderson, 2000; Gretzer et al., 2006; Luttikhuis et al., 2006; Anderson et al., 2008) (Fig. 3).

Following implantation of any foreign substance, components of both the acute as well as chronic inflammatory reactions may be elicited (Anderson, 2001). Proteins associated with the acute inflammatory response such as albumin, fibrinogen, complement, and others can readily attach to biomaterial surfaces after implantation (Jenny and Anderson, 2000; Keselowsky et al., 2007; Anderson et al., 2008; McNally et al., 2008). The surface characteristics of biomaterials can affect which of the inflammation-associated proteins bind to the surface of a biosensor, and thereby represents a mechanism for potential modulation of the ongoing inflammatory response to the device (Broughton et al., 2006). Chronic inflammatory responses may also develop in response to the biomaterial at the implantation site. Macrophages are a key cell mediator of the chronic response to implanted biomaterials, through their roles in foreign body giant cell formation (FBGC), and the production of degradative enzymes and inflammatory mediators such as reactive O₂ species (Henson, 1971a; Henson, 1971b; Anderson, 2000; Broughton et al., 2006; Castro et al., 2014); it is these reactions that can lead to biomaterial degradation and device failure (Haas, 2007; Anderson et al., 2008). Macrophages also elaborate numerous pro-fibrotic factors, which lead to formation of a fibrous capsule surrounding the biosensor (Song et al., 2000). The fibrous wall, combined with the FBGC, creates a barrier surrounding the implant which can lead to impaired function of the biosensor.

The majority of the literature related to the FBR focuses on materials that are implanted into normal tissue. However, one paper investigated the FBR using cotton thread implanted within rodent tumours compared to that seen in normal tissues (Mahoney and Leighton, 1962). They concluded that the response within the tumour was minimal compared to that seen in the normal tissues. Although more research is required on the effects of implanting devices directly into tumours, the results published in this paper indicated that the FBR may be decreased within tumours. This has important implications for the future use of implantable devices in cancer therapy.

Regulations governing implantable medical devices and challenges in bringing implantable biosensors to the clinic

In 1992 the International Standards Agency (ISO) was set up as a joint project between Canada, Great Britain and the USA. This organisation developed and published international standards on the Biological Evaluation of Medical Devices: ISO 10933, with implantable biosensors being classified as devices in contact with tissues for more than 30 days. The document describes methods for biocompatibility testing prior to clinical trials and includes

¹ See: Implantable Microsystems for Personalised Anti-Cancer Therapy. www.impact.eng.ed.ac.uk (accessed 22 July 2018).

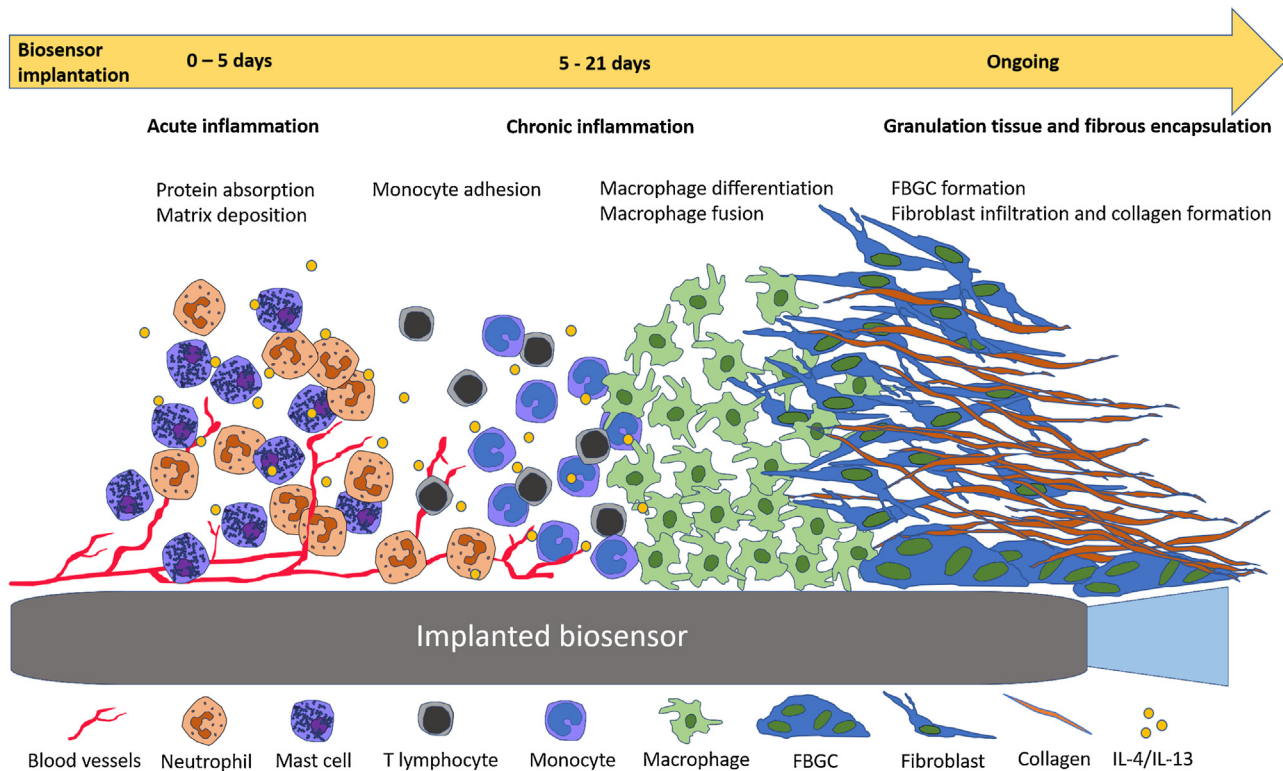


Fig. 3. Diagram outlining the stages of inflammation that occur following the implantation of a medical device/biosensor. These inflammatory phases include: tissue injury, blood–biomaterial interactions with provisional matrix formation, acute and chronic inflammation and the formation of granulation tissue with fibrosis/fibrous capsule development. Mast cells and PMNs are the predominant cell types present in the acute inflammatory phase, while macrophages drive the later inflammatory responses. The provisional matrix, formed by biomaterial adherent proteins, contributes to ongoing inflammation through cytokine, chemoattractant and growth factor release. These substances include: transforming growth factor beta, platelet-derived growth factor, CXCL4, leukotriene and interleukin-1. Within 2 days following implantation, PMN numbers decrease as they undergo apoptosis and are engulfed by macrophages. Macrophages enhance the propagation of the chemoattractive signals through the production of: platelet derived growth factor, tumour necrosis factor, IL-6, granulocyte-colony stimulating factor, chemokine (C-C motif) ligand 2 and granulocyte macrophage colony stimulating factor. The cytokines IL-4 and IL-13 are important factors in FBGC formation, enhancing monocyte adhesion, macrophage differentiation and fusion. The end result of the FBR is the production of granulation tissue with subsequent fibrous capsule formation. This reaction causes a ‘walling-off’ of the biosensor from its immediate surrounding area; this, combined with the degradative chemicals released from the FBGC, can lead to a loss of biosensor function.

suggested *in vitro* tests for cytotoxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, biofunctionality (adhesion, spreading, biosynthetic function), hemocompatibility and degradation assessment. *In vivo* assessment includes tests for local tissue effects after implantation, ethylene oxide residues, degradation of materials, irritation and sensitisation, along with systemic toxicity (ISO, 1992). The Food and Drug Administration has also been involved in the production of regulations specifically for the use of implantable biomaterials with drug release systems.

Although these *in vitro* tests are excellent for initial screening processes, animal models are required to evaluate tissue reactions. Various methods of *in vivo* biocompatibility testing have been developed, such as the cage implant system (Koschwanetz and Reichert, 2007), a chamber system (Papenfuss et al., 1979; Ertefai and Gough, 1989) and an avian chorioallantoic membrane (CAM) system of a developing chick embryo (Valdes et al., 2002; Valdes et al., 2003). These methods allow harvesting of tissue or fluid in the region of the implanted biomaterial, which can be analysed to assess the collagen capsule, inflammatory response and presence of capillaries.

Implantable medical devices must conform to regulatory bodies to ensure patient safety, with implantable biosensors coming under The Active Implantable Medical Devices Directive 90/385/ECC, developed by the Medicines and Healthcare products regulatory Agency. EU regulatory frameworks are undergoing revision after shortcomings identified within the system, which were highlighted by cases such as metal-on-metal hip implants and Poly Implant Prothese (PIP) breast implants. Manufacturers of

implantable medical devices must provide evidence of product safety and performance. However, clinical evidence is not always required; using ‘equivalence data’/published clinical work of similar devices can decrease the time in getting a product to market, but could potentially lead to safety concerns as each device is not fully evaluated. Once implants have gained market approval, post-market surveillance is required to pick up limitations/adverse incidents by patients, clinicians and manufacturers.

Human factor studies, which focus on the interactions between devices and people, are also applicable to veterinary patients. However, the opinions of patients or pet owners themselves can often be overlooked by researchers and clinicians, which has led to difficulties in the development of new technologies. For example, a lack of prior consultation with members of the deaf community with respect to cochlear implants meant that the development and use of this technology was met with patient resistance (Blume, 1999; Ramsden, 2013). Similar studies for implantable cardiac defibrillators have shown that device implantation can lead to significant psychological distress in patients (Duru et al., 2001; Ooi et al., 2016).

Veterinary-orientated human factor studies should help ensure that pet owners can use implanted devices (such as continuous glucose monitoring systems) safely and effectively, making informed treatment decisions based on sensor readings. The use of social scientists in the development of implantable medical devices is also important as they can be involved in the investigation of patient groups/pet owners to see if they would accept having devices implanted into their bodies/pets as part of

the treatment regime, while also evaluating the ethical implications of using these technologies (Ikegwuonu et al., 2015). The integration of these types of studies at the very beginning of any future projects would aid in a greater understanding of the disease process, and foster ways in which implantable sensor technology can be best developed to enhance patient treatment.

Conclusions

Since the development of the first glucose electrochemical sensor, technological advances in the fields of biocompatible material development, wireless power supply, miniaturisation techniques and bioengineering has led to a considerable amount of research focusing on the development of implantable biosensors, both with and without drug delivery systems. These devices could contribute significantly to the field of precision medicine; devices are being engineered to make continuous monitoring of patients possible, reducing the number of invasive interventions required and enabling drug treatments to be administered at specified times. Overall, implantable biosensors have the potential to improve the management of patient health and quality of life, increasing survival rates while reducing health care costs. Detailed genotypic and phenotypic analysis of individual patients is becoming more readily available and is happening in parallel to the development of new drugs and diagnostics. This will allow precision veterinary medicine to become a reality, but these advances still necessitate new technologies, such as implantable biosensors, to assess patients in real time. The development of implantable biosensors represents the intersection of engineering, chemistry, social science, medicine and veterinary medicine and underscores the importance of working across disciplines to advance patient care; these developments could accelerate a step change in the diagnosis and treatment of disease, supporting new initiatives in livestock species to underpin precision agriculture.

Conflict of interest statement

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